Effect of Kneading Disk Geometry on Twin-Screw Continuous Melt Granulation

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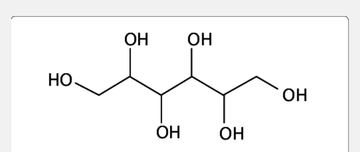
PURPOSE

The purpose of this study is to evaluate ***novel screw geometry*** on the twin-screw melt granulation process and granule properties. ***Twin-screw melt granulation***, relies on heat and ***mixing (dispersive and distributive mixing)*** at the kneading zone for granulation to occur. ***Kneading disc width (DW), staggering angle, and overflight clearance (OC)*** affect the mixing during processing. Rationale behind current design **(5 mm DW, 0.1 mm OC)** was to balance applied shear and elongational stresses for mixing coupled with forward movement of the material for polymer melt compounding. Melt granulation is not as intensive as melt compounding as only the binder melts while the drug remains as solid. ***Contributing stresses*** in the current design can be ***excessive for melt granulation*** leading to undesired physicochemical changes such as chemical degradation and polymorph changes etc. to drug substance. Radical changes to element design should be contemplated to broaden the scope of extrusion technology in particle processing.

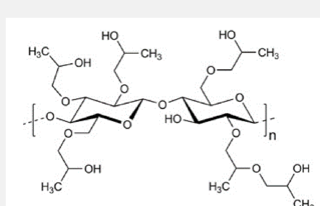
OBJECTIVE(S)

1. To evaluate the new kneading elements with reduced disc width ***(2, 4 mm)*** and increased overflight clearance ***(0.2, 0.3, 0.4 mm)*** in melt granulation of mannitol (model compound) using Klucel™ (hydroxypropyl cellulose) as the thermal binder on the granulation process.
2. To study the impact of new kneading elements on particle size distribution and tabletability of the processed granules.

METHOD(S)



Pearlitol™ (Mannitol)
(Model compound)



Klucel™
(Hydroxypropylcellulose [HPC])

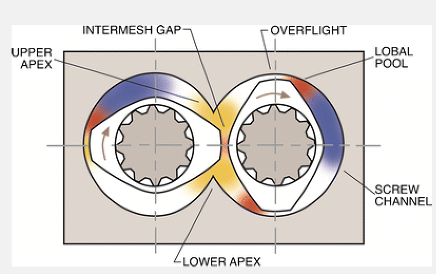


Fig. 1. Shear zones in kneading element cross-section

Preliminary trials:

1. Differential scanning calorimetry: Melting point depression and study miscibility of the physical mixture
2. Granulations run on Micro-18 using the current kneading elements (presented at AAPS 2021).

Twin-screw melt granulation:

Granulation trials were performed at 10% Klucel levels on a Leistritz ZSE-18 twin-screw co-rotating extruder. Feed rate was kept constant at 1.8 kg/hr. Barrel temperature, screw speed and screw configuration were varied.

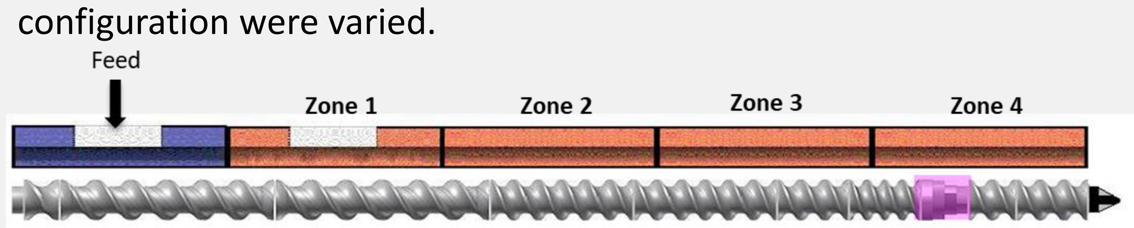


Fig. 2. Current screw configuration for twin-screw melt granulation

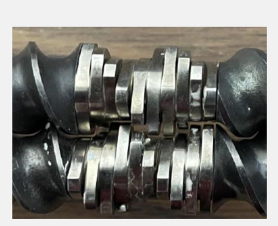


Fig. 3. New kneading block (2mm disc width elements)

Analytical characterization:

1. Tabletability of granules (250-600 µm) using single station hydraulic tablet press at 215 MPa compression pressure.
2. % Percent weight fraction of fines using a sonic sifter (Fines are defined as <150 µm).
3. Particle size distribution (PSD) using a Camsizer

RESULT(S) AND DISCUSSIONS

How to granulate with new kneading elements ?

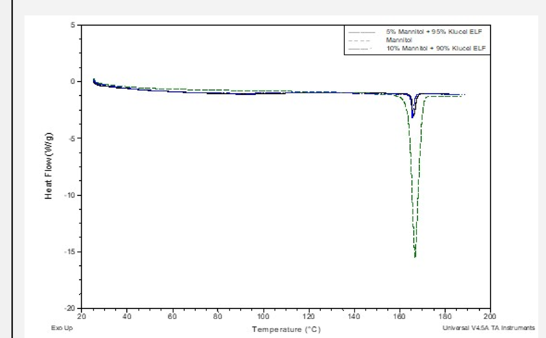


Fig. 4. DSC thermograms of Mannitol, Mannitol-Klucel physical mixtures

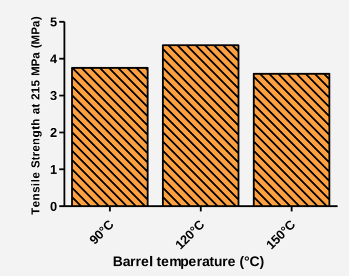


Fig. 5. Tensile strength of tablets(MPa) compressed from granules processed at 10% HPC level at different barrel temperature and screw speed of 100 rpm with current kneading elements.

Fig. 6. Visual images showcasing granulation with current kneading elements (5 mm disc width and 0.1 mm overflight clearance) staggered at 30 ° vs no granulation until 155 °C with new kneading elements staggered at 30°

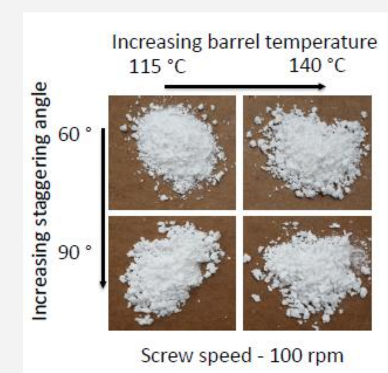


Fig. 7. Visual images showcasing granulation with new kneading elements (2 mm DW, 0.3 mm OC) at lower temperatures when staggered at higher angles.

- DSC thermograms (Fig. 2) indicated there was no melting point depression confirming mannitol-Klucel immiscibility.
- ***Granule formation and growth*** was observed for the current kneading elements ***across*** all barrel temperatures from ***90-150 °C*** for all screw speeds from 100-300 rpm at the staggering angle of 30°. (Fig 5).
- ***No granulation*** was observed even at the barrel temperature of ***150 °C*** with ***new kneading elements*** configured at the staggering angle of 30° (Fig 5)
- ***Higher barrel temperature (155°C)*** was required for ***granule growth with new kneading elements*** as compared to conventional pointing at reduced viscous dissipation.
- ***Barrel temperature*** can be ***reduced significantly (around 40 °C)*** by ***increasing the staggering angle*** to 60 or 90 ° while attaining granules with good tabletability and less fines at 100 rpm with new kneading elements.

Do new kneading elements promote granule growth ?

Table 1. Statistical analysis of % weight fraction of fines produced across different processing variables (p < 0.05 for significance). Fines are defined as <150 µm

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	37.293774	6.194187	6.02	0.0003*
Overflight clearance(0.2,0.4)	-8.598938	6.722118	-1.28	0.2367
Disc width(2,4)	7.2371973	6.194187	1.17	0.2763
Barrel Temperature(90,155)	-28.84617	6.719116	-4.29	0.0026*
Screw speed(100,400)	0.5671289	6.550107	0.09	0.9331
Overflight clearance*Disc width	7.9473125	6.722118	1.18	0.2710
Overflight clearance*Barrel Temperature	9.4273125	6.722118	1.40	0.1984
Disc width*Barrel Temperature	-6.756677	6.719116	-1.01	0.3441
Overflight clearance*Screw speed	-2.757313	6.722118	-0.41	0.6924
Disc width*Screw speed	1.9908789	6.550107	0.30	0.7689
Barrel Temperature*Screw speed	1.2043176	6.721113	0.18	0.8622

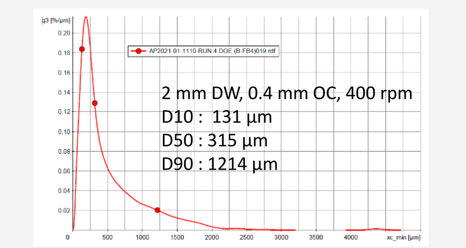


Fig 8. Monomodal PSD with narrow DW elements.

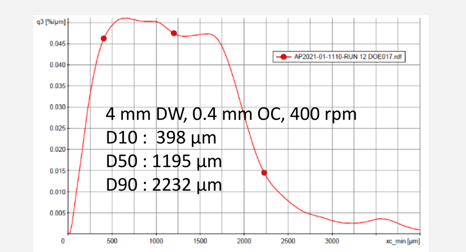


Fig 9. Broad multimodal PSD with wide DW elements.

- ***Barrel temperature*** had a ***significant effect on the % weight fraction of fines*** produced during the granulation process (p<0.05). (Table 1.)
- ***2mm DW*** produces a **more uniform and narrower *PSD*** as compared to ***4 mm DW (Fig 8 & 9)***
- ***4 mm DW*** promotes ***better granule growth*** than ***2 mm*** based on the D90 value determined from the Camsizer.
- ***At higher staggering angle***; low speed (100 rpm) required for granulation as ***higher speed*** (400 rpm) ***produces fines***.

Can the new kneading elements yield compressible granules ?

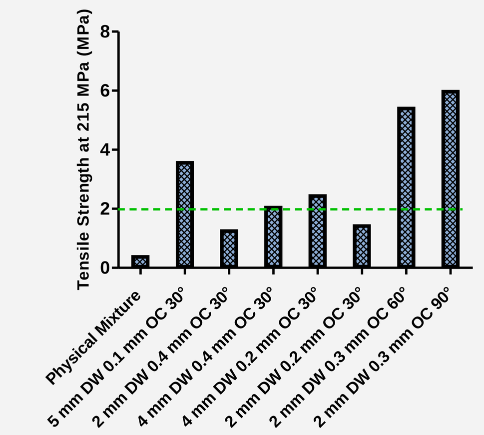


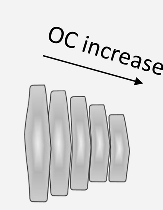
Fig 10. Tensile strength vs granules compression pressure (MPa) for granules processed at different conditions compressed on a single station hydraulic press at 215 MPa compression pressure.

Table 2. Statistical analysis of tensile strength of tablets compressed at 215 MPa across different processing variables. None of the processing parameters had a significant effect on the tensile strength.

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1.84	0.0625	29.44	0.0216 *
Overflight clearance(0.2,0.4)	-0.1125	0.0625	-1.80	0.3228
Disc width(2,4)	0.4425	0.0625	7.08	0.0893
Screw speed(100,400)	0.0475	0.0625	0.76	0.5863
Overflight clearance*Disc width	-0.14	0.0625	-2.24	0.2673
Overflight clearance*Screw speed	0.05	0.0625	0.80	0.5704
Disc width*Screw speed	0.015	0.0625	0.24	0.8500

- When staggered at 30°, ***new kneading elements*** resulted in the granules with ***poorer tabletability despite granule growth*** (Fig 10).
- ***Screw speed, DW, OC did not*** have ***any significant impact*** on the ***granule tabletability*** at the attested screw configuration with staggering angle of 30° (Table 2).
- ***Increased DW & reduced OC*** resulted in granules with ***better tabletability*** at a staggering angle of 30° with given screw configuration.
- ***Increase in the staggering angle*** from 30 ° to 60 or 90° significantly ***improved the tensile strength of the tablets*** (>5 MPa) while also producing less fines (< 6%) with the new kneading element. Higher staggering angle compensated for the lower shear stresses created by narrower disc and wider over flight clearance.

Novel screw configuration with new kneading elements



Schematic staggered block

Table 3. % weight fraction of fines produced and tabletability of granules processed with a 30° staggered kneading block (tight to wide OC i.e., 0.2 to 0.4 mm)

Disc width (DW)	Screw speed	% fines produced	Tensile strength at 215 MPa
2 mm DW	100 rpm	1.11	1.2 MPa
	400 rpm	10.85	0.74 MPa
4 mm DW	100 rpm	0.13	2.36 MPa
	400 rpm	2.31	2.36 MPa

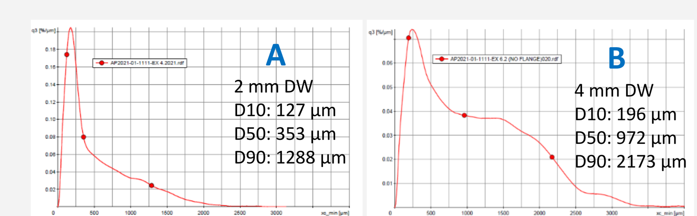


Fig 11. PSD of granules processed at barrel temperature of 155 °C and screw speed of 400 rpm staggered at 30° - (A) 2 mm DW (B) 4 mm DW.

- ***Staggered block*** can be used to attain monomodal PSD at narrow DW but worsens the tabletability of the granule.
- Future studies need to be carried out with higher staggering angle (60 or 90 °) or higher barrel temperature in a staggered block to elucidate if it can improve tabletability while maintaining a narrow PSD.

CONCLUSIONS

- ***Reducing kneading disc width*** and ***increasing the overflight clearance*** was found to ***reduce undesirable viscous dissipation*** which is otherwise detrimental to drug stability.
- ***However, higher barrel temperature is required*** for ***granule formation and growth*** with the new kneading elements than the current setup. ***Despite granule growth*** and higher barrel temperature, granules have ***poor tabletability*** pointing towards ***not enough mixing*** with new kneading elements at staggering angle of 30°.
- ***Increasing the staggering angle*** in the kneading block ***compensated for the reduced shear*** in the novel kneading elements to produce granules with good tabletability and low % weight fraction of fines at lower barrel temperature.
- Future experiments are planned using new kneading elements and gabapentin (which degrades on high thermal and mechanical stresses) to understand if the reduced peak shear with new kneading elements help reduce drug degradation during melt granulation while yielding good granule properties.

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